Argon laser photocoagulation for retinopathy of prematurity: long-term outcome

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Abstract

Purpose To assess the visual, refractive, ocular structural, and neurodevelopmental outcome in a group of children who were screened, treated with laser photocoagulation for threshold retinopathy of prematurity (ROP), and followed up at our institution.

Methods The 21 survivors of a cohort of 23 children were recalled at the age of 5 years or more. They underwent a full ophthalmologic examination. A paediatric neurologist and/or developmental paediatrician performed a neurodevelopmental assessment and a neuropsychologist performed psychological testing.

Results A total of 30 eyes (71.4%) had a best-corrected visual acuity (BCVA) of 20/40 or better. In all, 26 (62%) eyes were myopic; the overall mean spherical equivalent was −4.95 D. No eye had Stage 4 findings and only one eye (2.4%) progressed to stage 5 despite photocoagulation. In total, 14 patients (66.6%) showed evidence of stereopsis. Strabismus was seen in six patients (28.5%) and nystagmus in three (14.3%). Periventricular leukomalacia (PVL) was identified in five patients (23.8%), cerebral palsy (CP) in seven (33.3%), and intraventricular haemorrhage (IVH) in 13 (62%). Cerebral palsy and IVH associated strongly with visual acuity of less than 20/40 ($P = 0.009$ and 0.047). There was also a strong association between visual acuity of 20/40 or above and a better cognitive outcome ($P = 0.013$).

Conclusions Retinal scarring and detachment are relatively rare causes of visual morbidity 5 years or more after laser treatment for threshold ROP, but the neurological sequelae

of extreme prematurity and amblyopia remain important causes of impaired visual function.

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Introduction

Cryotherapy was shown to be beneficial for patients with threshold retinopathy of prematurity (ROP) by the Cryo ROP study.^{1–4} Since then, laser photocoagulation has largely replaced cryotherapy as the treatment of choice, with improved anatomical and visual outcomes.^{5–9} Laser photocoagulation is also thought to induce less myopia than cryotherapy.^{7,8,10–12} Nevertheless, ROP remains an important source of visual impairment in childhood and is one of the important treatable causes of blindness worldwide.^{13,14} In the United States and the developed world, ROP remains one of the three leading causes of paediatric blindness/severe visual disability.¹³ It is also an increasing problem in the developing world with the improving survival of low and very low birth weight infants.¹⁵

There is little information regarding the long-term visual outcome after laser treatment for ROP. We followed a cohort of patients for at least 5 years and wished to review their structural, refractive, visual, and neurodevelopmental outcome. Since posterior visual pathway factors related to neurological injury can affect vision in ROP,¹⁶ we also wished to review and analyse their possible contribution to the final outcome in this group of patients.

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Materials and methods

All the patients who underwent screening and subsequent treatment for ROP at our institution between March 1994 and May 1998 and who are now 5 years of age or older were eligible for this study. All the infants were screened at 6 weeks postnatal age by one of the authors (AM) and treated by another (CJL) under general anaesthesia within 48 h of recognition of threshold ROP as defined by the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity.¹

Confluent photocoagulation burns were applied to the nonvascularized retina anterior to the demarcation ridge, and all patients were seen at weekly intervals to ensure regression of the ROP after treatment. An HGM argon laser model 8 was used via indirect delivery at a wavelength of 514.5 nm.

All patients were recalled for a full ophthalmological examination. The best-corrected visual acuity (BCVA) was determined using the Snellen or HVOT letter recognition chart at 20 ft. In order to include all the data in the statistical analysis, any eye with no perception of light was assigned a visual acuity of 20/2000. Preferential looking acuities using Teller cards were used for the three patients who could not manage optotype acuities due to cognitive limitations, as shown in Table 1. The presence

of nystagmus was noted. Stereoacuity was assessed with the Titmus test and ocular alignment by cover and prism cover testing. Cyclopentolate 1% drops were instilled in each eye 30 min prior to retinoscopy. Indirect fundoscopy was performed with particular attention to the presence of the scarring sequelae of ROP including straightening of the major arcade vessels, macular distortion or dragging, hooding of the optic disc, and tractional retinal detachment. The visual fields were assessed using kinetic perimetry with a 40 cm arc perimeter, presenting the child a white foam ball of 4 cm in diameter, which is moved from the periphery towards the fixation target in at least four meridians (left, right, superior and inferiorly), testing each direction at least three times in a random order, as described by van Hof-van Duin *et al.*¹⁷

At a separate visit, each patient was seen by a paediatric neurologist (JJ) and/or developmental paediatrician (CM) from the Visual Impairment Program. In addition, patients were evaluated by a trained neuropsychologist using the WISC III-R to determine their intellectual function.¹⁸ Four patients could not be tested in this way due to significant mental handicap. Patients scoring low-normal or better (80+) would be expected to require less academic support and were therefore considered for the purposes of this study to have a good cognitive outcome. Conversely, those

Table 1 Functional outcome

Patient	BW	GA	Gender	BCVA		Spherical equivalent (D)		Sterealignment		VF loss (deg)
				Right	Left	Right	Left			
1	940	26	M	20/100	20/40	-16.00	-10.00	0	Normal	10-15
2	1335	30	F	20/20	20/20	-2.75	-3.12	200	Normal	<10
3	728	25	M	20/20	20/25	+1.00	+0.75	100	Normal	<10
4	1050	31	M	20/20	20/20	+0.50	+0.75	200	Normal	0
5	980	26	F	20/20	20/20	+0.75	+0.62	40	Normal	NA
6	1015	26	F	20/30	20/25	-6.50	-8.00	0	Normal	10-15
7	905	25	F	20/20	20/25	+0.75	0.00	80	Normal	<10
8	790	26	F	20/25	20/25	-4.00	-4.00	100	Normal	NA
9	855	27	F	20/20	20/20	+0.33	+0.75	60	Normal	NT
10	530	23	F	20/20	20/20	0.00	0.00	50	Normal	<10
11	873	25	M	20/50	20/60	-11.00	-13.00	0	ET	<10
12 ^a	720	23.6	M	20/400	Stage 5	-7.00	Stage 5	0	ET	40-50 ^b
13	650	24	F	20/40	20/20	-0.50	+0.62	800	ET	<10
14 ^a	945	26	F	20/80	20/80	+1.50	+2.75	0	ET	NT
15	565	24	F	20/25	20/30	-6.40	-2.25	100	normal	0
16	550	24	F	20/30	20/40	-7.50	-8.75	400	normal	<10
17	670	24	F	20/25	20/80	-8.25	-10.50	0	ET	0
18	975	26	M	20/40	20/30	-11.00	-10.50	100	normal	NA
19	730	25	F	20/25	20/20	-13.50	-10.00	200	normal	20
20	735	26	F	20/60	20/60	-7.40	-6.25	3000	normal	NT
21 ^a	855	27	F	20/200	20/200	-14.00	-12.00	0	HT	40-50

BCVA = Best-corrected visual acuity; GA = gestational age at birth, in weeks; BW = birth weight, in grams; ET = esotropia; HT = hypertropia; NA = not available; NT = not testable.

^aVA determined with Teller acuity cards.

^bTested in only one eye.

scoring borderline mental handicap or worse were classified as having a poor cognitive outcome. The patients who could not be tested with WISC III-R because of their mental handicap, were classified as poor cognitive outcomes for the purpose of analysis. Pearson's *R* was used to determine the strength of association between (a) the cognitive level and visual acuity, (b) cerebral palsy (CP) and visual acuity, (c) periventricular leukomalacia (PVL) and visual acuity, and (d) intraventricular haemorrhage (IVH) and visual acuity. In order to allow statistical handling of acuity values, the Snellen acuities were converted to logMAR. Also for statistical purposes, when analysing neurodevelopmental outcome, visual acuity of 20/40 or better in the best eye was considered a good visual outcome, and visual acuity of less than 20/40 a poor visual outcome.

Results

In total, 23 infants were treated with bilateral argon laser photocoagulation to the peripheral nonvascularized retina between March 1994 and May 1998. Two of these died before the age of 6 months (deaths not related to ROP laser treatment); until that time, their retinas had been recorded to be attached. The information on these two patients was excluded from the analysis, leaving a total of 21 patients (42 eyes) in this study. All these (100%) were recruited and reviewed. There were 15 female and six male patients whose average chronological age at the time of follow-up was 6.2 years (range: 5–7.6). The mean gestational age at birth was 25.7 weeks (range: 23–35) and mean birth weight was 828 g (range: 530–1335). Of the 42 eyes, 40 (95%) had had at least 5 contiguous or 8 cumulative clock hours of stage 3+ disease in zone II at the time of treatment; the two eyes (5%) of patient no.12 had zone I rush disease. Laser treatment was performed bilaterally in all cases, at a mean of 34.6 weeks postmenstrual age (range: 31.4–38.2 weeks). Lack of regression of ROP despite treatment was observed in five patients 1 week after the initial treatment, and they underwent repeat laser photocoagulation. In four of these patients, the disease then regressed but in one (patient no. 12) continued progression was noted.

Visual and refractive outcome

Of the 42 eyes, 30 (71%) achieved a BCVA of 20/40 or better and 14 (33%) a BCVA of 20/20. Overall, the mean visual acuity was 20/98. When the only eye with retinal detachment was excluded, the mean visual acuity in the group was 20/52. This information is summarized in Table 1. Six patients had strabismus (28.5%) and three

Table 2 Anatomical outcome

Patient	Vascular straightening	Macular distortion	Disc hooding
1	R		
4	RL		
9	RL		
11	RL	RL	RL
12 ^a	R	R	R
14	RL		
18	RL		
20	R	R	
21	R		

R = right eye; RL = both eyes.

^aRetinal detachment in the left eye.

nystagmus (14.3%). Four patients were treated for amblyopia. In three of them, anisometropia and strabismus were present, and in one other, only strabismus was present. Stereopsis was present in 14 patients (66.6%).

The overall average refractive spherical equivalent (SE) after laser photocoagulation was -4.95 D (range: -16.0 to $+2.75$). Of the 42 eyes, 26 (62%) were myopic, 20 (47.6%) with a spherical equivalent greater than -4.0 D. The refractive outcome is shown in Table 1. The astigmatism ranged from 0 to 3.5 D (mean 2.0 D). In all, 26 eyes (62%) had with-the-rule astigmatism and only one eye (2.4%) against-the-rule. Two patients had a difference greater than 1 D between the degree of astigmatism of their eyes.

Visual fields were available in 29 eyes of 15 patients. In 24 (83%) eyes, the reduction of visual field was minimal, in the order of 15° or less. Individual visual field results are also presented in Table 1.

Anatomical outcome

Of the 42 treated eyes, one progressed to stage 5 ROP despite treatment (2.4%). None of the treated eyes had stage 4 findings or macular folds at follow-up. Some degree of macular distortion was seen in four eyes. The anatomical outcome is summarized in Table 2.

Neurodevelopmental outcome

Neurological problems were common in this series; of 21 patients, 13 had IVH (62%), seven CP (33.3%), and five PVL (23.8%). Of these disorders, CP was the most likely to be associated with poor visual outcome as described above, although this was not invariably the case. Three out of 16 (19%) children with good visual outcome had CP, compared to four out of five (80%) who had a poor visual outcome ($P = 0.009$). IVH was also associated with poor vision, since all the five children with poor visual outcome (100%) had IVH, compared to eight of 16 (50%)

Table 3 Neurodevelopmental outcome

Visual acuity	Cognitive outcome		
	Good	Poor	Total
≥20/40	10	6	16
<20/40	0	5	5
Total	10	11	21

with good visual outcome ($P=0.047$). Three out of 16 (19%) children with good visual outcome had PVL, compared to two out of five children (40%) with poor visual outcome ($P=0.35$).

In addition, psychoeducational testing documented 11 children who scored in the borderline range ($IQ<80$) or worse, and Pearson's R demonstrated an association between poor cognitive outcome as defined above and visual acuity worse than 20/40 ($P=0.013$). See Table 3.

Discussion

The Cryo-ROP study showed the beneficial effect of treatment on visual acuity and anatomic status at 10 years follow-up.¹⁹ Laser photocoagulation has replaced cryotherapy as the standard treatment in most centres. The diode laser is now also widely used, although the outcome of this modality is not considered by this study. More recently, threshold criteria for treatment have been re-evaluated.²⁰ However, few studies of long-term outcome after laser treatment are available: Two of the 23 eyes treated with laser by Ng *et al*, had developed stage 5 ROP at 10-year follow-up evaluation.⁵ Shalev *et al*²¹ followed up 10 eyes treated with laser for ROP for 7 years; none of these developed stage 5 ROP although one patient who had an unfavourable outcome in the laser treated eye died before follow-up. In our study, only one eye of 42 (2.4%) developed a total retinal detachment. Although two infants died before the age of 6 months and were therefore excluded from the study, neither had retinal detachment prior to their death. Other authors have reported favourable structural outcomes as defined by the Cryo-ROP study after laser treatment, with shorter follow-up times.^{9,22–25}

It is interesting to note that the only child who developed stage 5 ROP in our series had documented progression of severe rush disease in zone I despite two sets of laser photocoagulation to each eye. Only one of his eyes was judged by the vitreoretinal surgeon to have visual potential and therefore underwent vitrectomy. At follow-up, this eye had become phthisical; the contralateral (unoperated) eye retained a flat but severely distorted retina with a visual acuity of 20/400. In the

Cryo-ROP study, disease in zone II resulted in fewer unfavourable outcomes in both treated and control eyes than zone I disease.^{2,3} The severity and posterior location of the disease in the eye that developed stage 5 in our series likely contributed to the poor outcome. Macular ectopia was, as expected, a factor contributing to poor visual outcomes in patients 11, 12, and 20 in our series.

A high prevalence of myopia has been reported in premature babies.^{26–29} Prematurity in the absence of ROP has also been associated with a higher prevalence of myopia.^{29–31} Previous studies have found a positive correlation between myopia and more severe degrees of ROP,^{27,32,33} and O'Connor *et al*³⁰ reported that the prevalence of myopia in prematurely born children re-examined at 10–12 years of age increased from 22% in those with no ROP to 80% in those with ROP stage 3/4. Children with stage 1 and 2 disease did not differ from those with no ROP. Several authors have reported lower degrees of myopia after laser than cryotherapy treatment.^{7,8,10–12,34} Myopia was present in 62% of eyes in our series; the mean spherical equivalent of our patients (-4.95 D) was similar to that found in other series of children older than 3 years, in which the mean ranged from -3.05 to -6.5 D.^{7,8,21,35}

The Cryo-ROP study showed that 44% of eyes treated had vision of 20/200 or worse at 10-year follow-up, compared to 62.1% of eyes that were not treated. The same study reported visual acuity of 20/40 or better in 25.2% of treated *vs* 23.71% of nontreated eyes.¹⁹ Smaller comparative studies have found good visual outcomes in the group of eyes treated with laser.^{9,21} An overall mean visual acuity of 20/98 in 42 eyes of our study constitutes functional success, particularly because 30 eyes (71%) achieved final vision of 20/40 or more and 14 eyes (33%) saw 20/20 at follow-up. The mean age of patients in this study was slightly lower than in the Cryo-ROP study, possibly reflecting the fact that neonatal care has improved since that study was done.

A reduction of 5–7° in the peripheral visual field was reported at the 10-year examination of the treated Cryo-ROP patients.³⁶ Laser photocoagulation of both peripheral retinas to mid- or posterior zone II, as was necessary in some of the patients in this study, would be expected to cause significant peripheral visual field restriction; visual fields were only available in 29 of the 42 eyes in this study and formal testing using the Goldmann perimeter was not attempted due to the patients' young age. Nevertheless, in 24 eyes the visual field reduction was subtle, judged to be in the order of 15° or less. We felt overall that it did not impact function significantly.

Infants with extremely low birth weight are at risk of neurological abnormalities, developmental and functional delay.³⁷ A child's visual function is the result

not only of their visual acuity, field, and eye movements but also their cognitive level, motor skills and other factors. Msall *et al*³⁸ examined the relationship between ROP and the subsequent neurodevelopmental function in patients from the Cryo-ROP study at age 5.5 years. They found that disability increased from 3.7% among patients with no ROP, to 19.7% in those with threshold ROP, and identified ROP as a marker for disability. We focused our assessment on intellectual performance and the presence of neurological factors related to prematurity. We evaluated the cognitive level by determining the intellectual function, and found an association between poor visual outcome and the presence of cognitive impairment. Recently, Cooke *et al*³⁹ have reported the outcome of a cohort of children whom they have followed since 1991–1992. In their study, the eight children with stage 3 ROP had poorer scores on the Movement ABC and total and verbal IQ, but these differences were of borderline significance after standardizing for gestational age. They suggest a trend which would indicate stage 3 ROP to be a marker for adverse development. Although our study of 21 patients with stage 3 ROP lacked a control group, 11 children had a cognitive handicap (IQ < 80) and seven had CP.

The significance of IVH for long-term visual morbidity has been highlighted by previous studies^{40,41} and Lanzi *et al*⁴² found that visual impairment correlated with MRI findings of PVL in children affected by CP. We found that IVH and CP were associated with poor visual outcomes in the study group. In our series, only five patients were found to have PVL, and its presence was not significantly associated with decreased vision, although this could be due to the small numbers in the sample. While we realize that converting Snellen acuities to logMAR is an approximation, this was necessary to allow statistical analysis of our neurodevelopmental findings.

The results of this study show that at age 5 or above, patients who received confluent retinal argon laser photocoagulation for proliferative ROP have a satisfactory visual outcome since over three-quarters of them (76.19%) have binocular vision of 20/40 or better. Myopia is frequent. Laser therapy is effective in achieving a good structural outcome, with only one eye progressing to stage 5 disease. Although a poor visual outcome is sometimes due to retinal distortion, scarring or detachment due to the progression of ROP, this complication is becoming less frequent, accounting for five eyes of three children in this series. Some patients did not achieve good vision despite a good anatomical outcome. Their limited visual outcome was attributed to PVL in two patients (nos. 14 and 21), and unilateral amblyopia two patients (nos. 1 and 17). As a cause of visual morbidity, these factors are now almost as frequent as the scarring sequelae of ROP.

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